REMARKS

Claims 1-11, 14-21 and 23-24 are currently pending. Claims 12, 13, 22 and 25-56 have been withdrawn from consideration as being drawn to a non-elected invention. Applicants have formally cancelled these claims without prejudice or disclaimer of the subject matter contained therein and reserves their right to pursue these claims in a divisional application.

Rejections Under 35 U.S.C. § 103

The Examiner has issued two obviousness rejections. In the first rejection, the Examiner has rejected claims 1-11, 14-21 and 23-24 as unpatentable over either Hong (US 4,622,392), Hong (US 5,484,911) or Peterson (US 5,827,836) in combination with Janjic (US 6,229,002) and Vermehren (BBA, 1998). In the second rejection, the Examiner has maintained the rejection of claims 1-11, 14-21 and 23-24 as obvious over Kozak (USP 6,166,089) in combination with Janjic (USP 6,229,002) and Vermehren (BBA, 1998). These rejections are traversed and discussed in more detail below.

The Present Invention

The present invention is directed to a novel drug delivery system which employs polymer covered liposomes composed of anticancer lysolipid prodrugs for the treatment of cancer. The toxic anticancer drug constitutes the lysolipid part of a phospholipid prodrug with an acyl-linked fatty acid chain in the sn-2 position. The acyl-linked fatty acid in the sn-2 position inactivates the toxic effect of the anticancer lysolipid until this organic radical is hydrolytically cleaved off from the prodrug lipid by the action of extracellular phospholipase A2 (PLA2). The resulting lysolipid then becomes the active anticancer drug. By combining the anticancer lysolipid with an acyl-linked fatty acid of at least 7 carbon atoms in the sn-2 position, it becomes possible to

formulate prodrug lipids as liposome formulation. This is not disclosed or suggested by any of the prior art references cited by the Examiner, either singly or in combination.

The Legal Standard

As a preliminary matter, Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Three criteria must be met to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. Second, there must be a reasonable expectation of success. And, third, the prior art reference (or references) when combined must teach or suggest all of the claim limitations (*see* MPEP §2142).

The Examiner has acknowledged that none of the cited references anticipate the present invention. That is to say, none of the references disclose each and feature of the claimed invention. The Examiner, however, argues that certain combinations of the references disclose all of the elements of Applicants' claimed invention. It is axiomatic that the Examiner must identify the suggestion or motivation to combine the references and must also demonstrate that the prior art references, either singly or in combination, teach each and every claim limitation to substantiate the obviousness rejection. This the Examiner has not done.

Although the Examiner has identified passages within the references to establish the presence of certain limitations, the Examiner has failed to identify any suggestion, teaching or motivation within the references to modify the prior art references to arrive at the present invention. The Examiner merely states that it would have been obvious to do so. No evidence is proffered to support the Examiner's position.

Applicants acknowledge that the evidence of a suggestion, teaching or motivation may flow from the prior art references themselves or may flow from the knowledge of one of ordinary skill in the art. However, it is well settled that broad conclusory statements regarding the teachings of multiple references or the knowledge available to a person of skill in the art, standing alone, are not "evidence" (see *In re Dembiczak*, 50 USPQ2d 1614, 1617 (CAFC 1999)). The Examiner is required to cite a reference is support of his or her position.

The determination of whether an invention is obvious is a factual inquiry. In the instant case, the Examiner has not identified any teachings within the references themselves or within the general knowledge available to a person of skill in the art which would motivate them to combine or modify the references to arrive at the present invention. Instead of identifying the factual evidence that would support a finding of obviousness, the Examiner merely concludes that it would have been obvious to a person of skill in the art to use claimed polymer covered liposomes composed of anticancer lysolipid prodrugs in a lipid based drug delivery system. This is a classic case of hindsight reasoning wherein that which only the inventor taught is used against its teacher. *Id.* citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

The Examiner's conclusory statements regarding what would be obvious or within the "common knowledge" of a person of skill in the art are not a substitute for evidence. As noted by the court in *In re Lee*, the factual question of motivation is material to patentability and cannot be resolved on subjective belief and unknown authority (see 61 USPQ2d 1430, 1434 (CAFC 2002). The Examiner has failed to provide the factual evidence required to support a finding of obviousness.

1. Rejection in view of Hong ('392), Hong ('911) and Peterson ('836) in combination with Janjic ('002) and Vermehren (BBA, 1998)

In the first obviousness rejection, the Examiner has rejected all of the claims as being unpatentable over either Hong ('392), Hong ('911) or Peterson in combination with Janjic ('002) and Vermehren (BBA, 1998). The Examiner argues that the Hong and Peterson references each disclose phospholipid prodrugs wherein the carbon 1 of the glycerol has an aliphatic chain and the carbon 2 has an organic radical and carbon 3 has a phosphatidyl group. The Examiner cites to various portions of these references to support his argument that these references also teach that the phospholipids can be in the form of liposomes. The Examiner acknowledges that these references lack the teachings of the inclusion in a lipopolymer. The Examiner turns to the Janjic and Vermehren references which allegedly provide this missing element. Janjic is cited for disclosing lipid constructs containing PDGF and the attachment of PEG to the liposomal surface to shield the complex from blood proteins. Janjic also describes prodrugs on the outside surface of the liposome. Vermehren is cited for disclosing liposomes containing PEG which "optimizes the in vivo degradation of drug loaded liposomes at certain cites, e.g., in extravascular inflammatory tissue due to an enhanced local concentration of the active PLA2 and an accumulation of polymer-grafted liposomes in such tissues". The Examiner, therefore, concludes that it would have been obvious to one of ordinary skill in the art to use the PEG containing liposomes described in Vermehren or Janjic to deliver the prodrugs of Hong or Peterson because of the advantages of the liposomes and the ability of PEG to prolong the circulation time of the liposomes and increase their susceptibility to PLA2 in the host

pathological tissue thereby increasing the release of the drug attached to the carbon 2 of the phospholipids. Applicants respectfully disagree.

The present claims are directed to a lipid based drug delivery system, which has the following components and/or features:

a) a lysolipid derivative as the active substance

b) the active drug present in the form of a prodrug

c) the prodrug comprising an aliphatic group having at least seven carbon atoms, an organic radical having at least 7 carbon atoms and a hydrophilic moiety

d) the lipid prodrug, including the lipolymer and glycolipid prodrugs, are extracellular substrates for extracellular PLA_2

e) the PLA_2 cleaves the organic radical but not the aliphatic group off of the prodrug

f) the active drug is liberated as a lysophospholipid

g) the lysolipid is not a substrate for lysophospholipase

h) the drug delivery system includes lipopolymers or glycolipids as lipid prodrugs.

Applicants would first like to address the Examiner's characterization of the Hong and Peterson references. It should be noted that both of the Hong references disclose <u>different compounds</u> than those used in the present invention. It should also be noted that of these three references, only Hong ('911) mentions PLA_2. But, Hong ('911) fails to describe the exact mode of action or the effect of PLA_2. A review of the Hong ('911) suggests that the cleavage of the lipid conjugate takes place <u>within</u> the cell by intracellular cystolic PLA_2. However, it is clear

that Hong ('911) fails to describe the use of an inactive prodrug that can be activated by the release of the active drug in the form of a lysolipid.

Neither of the Hong references (or the Peterson reference) describe the mechanism involved in the instant invention, namely extracellular degradation of the polymer covered prodrug liposomes that accumulate in the extracellular intestinal space and become degraded by extracellular (secretory) PLA_2. In contrast, Hong ('392) teaches penetrability of tumor cells and phospholipid-enzyme specific reactions within the cell and Hong ('911) discloses large concentrations of conjugate entering the cell and the degradation/metabolization of the conjugate within the cell. Looking at the features of the invention set forth above, Applicants submit that Hong ('911), Hong ('392) and Peterson fail to disclose features (a) and (d) through (h). Accordingly, Applicants submit that a person of ordinary skill in the art would not be motivated to combine the teachings of Hong ('392), Hong ('911) or Peterson with the teachings of Janjic and Vermehren to arrive at the present invention.

2. Rejection in view of Kozak ('089) with Janjic ('002) and Vermehren (BBA, 1998)

The Examiner has again rejected claims 1-11, 14-21 and 232-24 as unpatentable over Kozak in combination with Vermehren. The Examiner contends that Kozak discloses phospholipid prodrugs where carbon 1 of the glycerol has an aliphatic chain, the carbon 2 has an organic radical and carbon 3 has a phosphatidyl group. The Examiner indicates that Kozak teaches the organic radical is released by phospholipase A2 (PLA_2) present in the pathological tissue. The Examiner acknowledges that Kozak lacks the teaching of a lipopolymer and the administration of the composition in the form of liposomes. The Examiner then argues that

Janjic and Vermehren teach this missing element. The Examiner's characterization of these two references has been described above. The Examiner concludes that it would have been obvious to a skilled artisan to use PEG containing liposomes for the delivery of the prodrug described by Kozak because of the advantages of liposomes and the ability of PEG to prolong the circulation time of the liposomes. He also contends that this would increase the liposomes susceptibility to PLA2 in the host pathological tissue and increase the release of the drug attached to carbon 2 of the phospholipid as described in Kozak. Applicants respectfully traverse.

Applicants' previous arguments in response to this rejection have been considered but found unpersuasive. Applicants had previously argued that Kozak teaches away from formulating the prodrugs into liposomes because the prodrugs have to be able to penetrate the cell wall as monomeric lipid prodrugs. In fact, Kozak teaches increased intracellular delivery of the monomeric lipid prodrug followed by cleavage by intracellular (cystolic) PLA_2. The Examiner rejected this argument finding that the reason Kozak did not use liposomes was because liposomes are taken up by the RES (reticuloendothelial system). The Examiner's comment clearly indicates that Kozak teaches against the use of liposomes. However, the Examiner still argues that the general art known advantages of liposomes (see pages 5-6 of the Office Action) would motivate a person of ordinary skill in the art to use liposomes with the Kozak compounds. This is a circular argument. Applicants submit that a person of ordinary skill in the art would not be motivated to combine the teachings of Kozak with Janjic or Vermehren because Kozak explicitly teaches that the use of liposomes is not preferred.

Once again, Applicants would like to point out that there are numerous differences between Kozak and the claimed invention apart from the absence of a lipopolymer and the

administration of the compositions in the form of liposomes. Referring to the list of features presented above, it is clear that Kozak fails to describe features (a), (d), (f), (g) and (i). Applicants had previously pointed out that the prodrugs disclosed in Kozak have acyl-linked groups on both carbon 1 and carbon 2, whereas the anticancer lysolipids have ether linked groups on carbon 1 and carbon 2. Moreover, Kozak teaches that intracellular PL2 will be able to hydrolyze diacyl phospholipids, but there is no indication or suggestion that this would also be true for the hydrolysis of phospholipids with, for example, ether-linked alkyl chains in the sn-1. Our attempt to distinguish the instant compounds from the Kozak compounds were considered but rejected by the Examiner the claim language did not exclude the Kozak compounds. Applicants respectfully disagree. Applicants would like to specifically direct the Examiner's attention to feature (g) which states that the lysolipid is not a substrate for lysophospholipase. This necessarily means that an acyl-linked group cannot be in position 1 because lysophospholipase cleaves acyl-linked groups not ether linked groups. As such, Applicants believe that the claim language does exclude the Kozak compounds.

The features of the present invention that are missing from Kozak are not disclosed in Janjic and Vermehren. Janjic relates to a DNA-ligand attached to PEG resulting in improved pharmacokinetics, whereas Vermehren discloses enhanced hydrolysis of PEG containing liposomes. Neither of these references discloses using the anti-cancer lysolipids as part of the lipid prodrug. As such, Applicants submit that a person of ordinary skill in the art would not consider the instant invention obvious in view of these references, either singly or in the combination asserted by the Examiner.

Conclusion

To conclude, Applicants submit that these references cited by the Examiner fail, either singly or in combination, to disclose each and every one of the features described above. Even if one were to assume that all of the features could be found, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness because the Examiner has failed to identify the teachings, suggestions or expectation of success within the references themselves to modify or combine them in such a way as to arrive at the present invention. The Examiner's statements regarding the art known advantages, etc. are conclusory statements that do not find basis in any of the references but merely seem to reflect the Examiner's own opinion. In other instances, the Examiner has taken Applicants' own teachings to provide the necessary motivation or incentive. This is improper and cannot be used to support an obviousness rejection. In view of this and the discussion above, Applicants respectfully request reconsideration and removal of the rejections.

In view of the foregoing remarks, all of the claims remaining in the case are submitted as defining non-obvious, patentable subject matter.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at 714-708-8555 in Costa Mesa, CA to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for an extension of one (1) month to July 6, 2003 for the period in which to file a response to the Office Action dated March 6, 2003.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Kalpana Kotwal #46,183
Leonard R. Svensson (#30,330)

P.O. Box 747
Falls Church, VA 22040-0747
(714) 708-8555

LRS/KR
2081-0113P

Attachments: Claims as Amended

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: July 7, 2003
(Date of Deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan M Dangwoothy
(Signature)

July 7, 2003
(Date of Signature)